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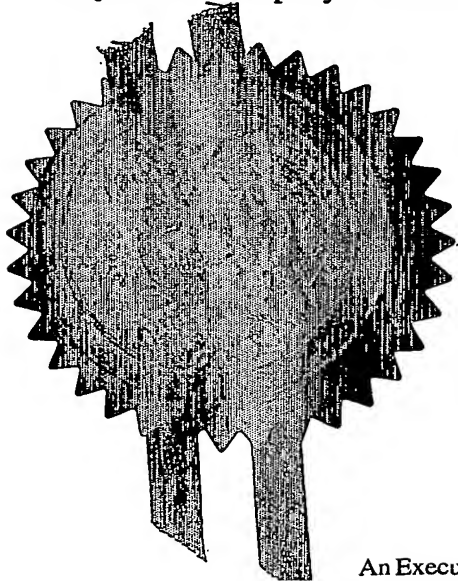
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Request for grant of a patent

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1. Your Reference	PF4879	12 JUL 2002	
2. Patent application number (The Patent office will fill in this part)	15 JUL 02 1733077 1 001030 P01/7700 0.00-0216233.7		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	<p>GLAXO GROUP LIMITED 980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS</p> <p>GLAXO WELLCOME HOUSE BERKELEY AVENUE GREEN FORD MIDDLESEX UB8 3NN 47857006</p>		
Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its corporation	GB 20/77 10.10.02		
4. Title of the invention	COMPOUNDS		
5. Name of your agent (if you know one)	JANETTE Y ROWDEN		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	<p>GLAXOSMITHKLINE 980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS</p> <p>8366817001</p>		
Patents ADP number (if you know it)			
6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of Filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day / month / year)
8. Is a statement of inventorship and of right to grant a patent required in support of this request? (Answer yes if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body.	YES		

See note (d))

Patents Form 1/77

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Continuation sheets of this form

Description	41
Claim(s)	3
Abstract	3
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Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patent Form 9/77)

Request for substantive examination (Patent Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application

Signature JANETTE Y ROWDEN
AGENT FOR THE APPLICANTS



12. Name and daytime telephone number of person to contact in the United Kingdom
LYNNE SAWKINS
020 8047 4461

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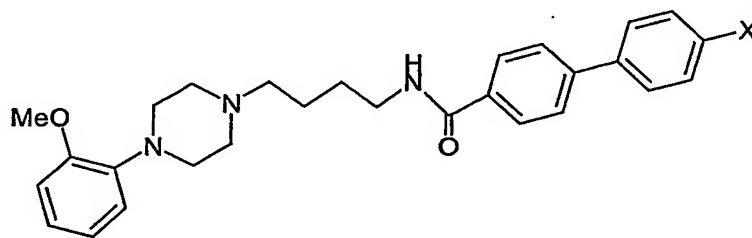
Therapeutic Aryl Piperidine Derivatives

This invention relates to novel compounds which up-regulate LDL receptor (LDL-r) expression and to processes for their preparation, pharmaceutical compositions containing them and their medical use. More particularly, this invention relates to novel aromatic piperidines and their use in therapy.

Epidemiological studies have clearly demonstrated the correlation between reduction in plasmatic LDL cholesterol and the benefit on cardiovascular events including mortality. LDL cholesterol is eliminated from plasma by specific binding to LDL-r expressed by the liver. Regulation of LDL-r expression occurs in the liver and is mainly dependent on intracellular cholesterol concentration. Increasing free cholesterol concentration leads to a reduced LDL-r expression through a mechanism involving transcriptional factors. Counteracting with this process is expected to up-regulate LDL-r expression in the liver and to increase the clearance of LDL cholesterol.

International Patent Application Number PCT.EP00.06668 concerns the novel use of the SREBP-cleavage activating protein (SCAP) in a screening method, and two compounds are disclosed, namely 4-(4-chloro-benzoylamino)-N-{4-[4-(2-ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-benzamide and 4-(4-Benzoyl)-N-{4-[4-(4-isopropyl-2-methoxy-phenyl)-piperidin-1-yl]-butyl}-benzamide hydrochloride, which do not form part of the present invention.

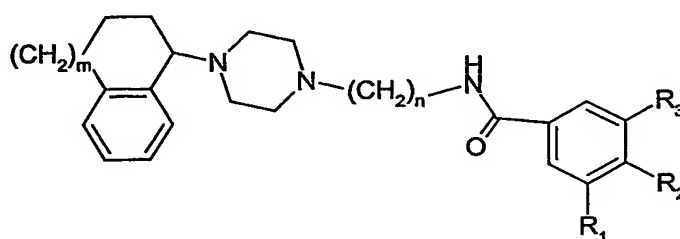
Another publication, Bioorganic and Medicinal Chemistry Letters Vol. 5, 3, 219-222, 1995 discloses compounds having the general formula (A)



A

where X may be COMe, SO₂Me and NH₂, as having high affinity for the dopamine D₃ receptor and postulates their use in CNS disorders, particularly psychiatric illness. The compound of formula A where X is COMe is also disclosed in J.Pharmacol. Exp. Ther. 287; 1 1998 187-197 and Bioorganic and Medicinal Chemistry Letters Vol. 7, 15, 1995-1998, 1997, again as being useful in treating CNS disorders. It will be noted that the examples of the present invention differ from those of formula (A) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

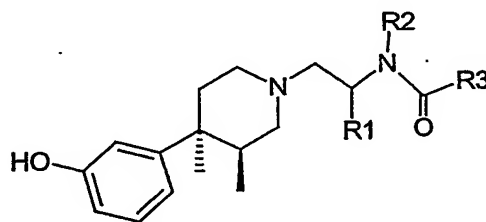
- 10 Journal Of Medicinal Chemistry, Vol. 40, 6, 952-960, 1997 discloses compounds of formula (B)



B

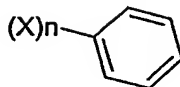
15 where $m=0,1$ or 2 ; $n=2$ or 3 ; R_1 and $\text{R}_3=\text{H}$ or OMe and R^2 may be Ph, as selective 5-HT_{1A} receptor ligands having CNS activity. It will be noted that the examples of the present invention differ from those of formula (B) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

20 International Patent Application Publication Number WO99/45925 discloses compounds of formula (C)



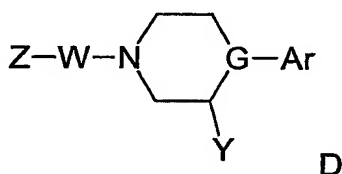
C

25 where R_1 may be hydrogen, R_2 may be hydrogen and R_3 may be a group



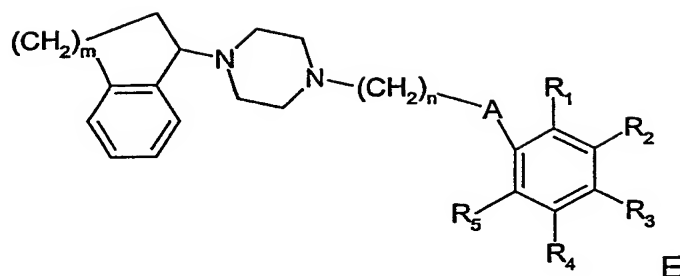
where X may be an aryl group and n may be 1. Specifically disclosed are compounds where the group COR3 is formed from 2- and 4- biphenyl carboxylic acid and R1 and R2 are methyl or hydrogen respectively. The utility of the compounds is as opioid receptor binding agents which may be useful as analgesics. The substitution on the 3- and 4- positions of the piperidine ring leave the compounds of this publication outside the scope of the present invention. Furthermore, the utility disclosed is different.

International Patent Application Publication Number WO98/37893 discloses compounds of formula (D)



where Ar may represent an optionally substituted phenyl or naphthyl, G may be N or CH₂ (*sic*), W may be an optionally substituted alkylene, Y may be hydrogen and Z may represent a group R₄CONR₅, where R₄ may be an optionally substituted phenyl and R₅ may be hydrogen. These compounds are described as being D2 receptor antagonists useful in the treatment of CNS disorders such as Parkinson's Disease. None of the compounds specifically disclosed fall within the scope of the present invention and the disclosed utility is different.

International Patent Application Publication Number WO9402473 discloses compounds of formula (E)

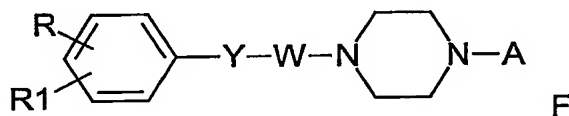


where A may be NHCO or CONH; R_1 - R_5 may be hydrogen or a benzene ring, m may be 1-3 and n may be 1-3. Specifically disclosed are the following compounds:

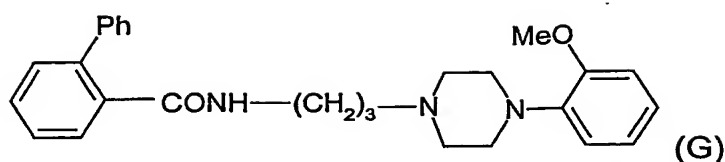
No.	A	n	m	R_1	R_2	R_3	R_4	R_5
5	NHCO	2	1	H	H	Ph	H	H
12	NHCO	2	2	H	H	Ph	H	H
19	NHCO	2	3	H	H	Ph	H	H

The compounds are described as 5HT-1A agonists having CNS activity and may be used as anti-depressants, anti-hypertensive, analgesics etc. It will be noted that the examples of the present invention differ from those of formula (E) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO99/45925 discloses compounds of formula (F)

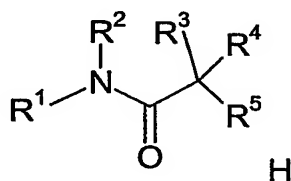


where A may represent a substituted phenyl group, W represents a linear or branched alkylene group having from 2 to 6 carbon atoms; Y may represent a group NHCO or CONH; and R may be a substituted phenyl group. Particularly disclosed is the compound G

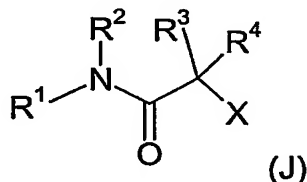


These compounds are described as being $\alpha 1A$ -adrenergic receptors useful in the treatment of contractions of the prostate, urethra and lower urinary tract, without affecting blood pressure. It will be noted that the examples of the present invention differ from those of formula (G) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO98/35957 describes compounds of formula (H)



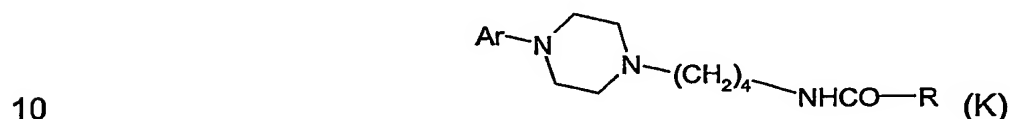
wherein R1-R5 are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkylalkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, nitro and cyano. Specifically disclosed compounds are those formed by the N-alkylation of a substituted piperidine or piperazine with a group (J)



where X is a leaving group. None of the compounds specifically disclosed fall within the scope of the present invention and the invention is in no way suggested by the disclosure. The compounds are said to be of use as NPY Y5 receptor antagonists in the treatment of obesity, bulimia and related disorders

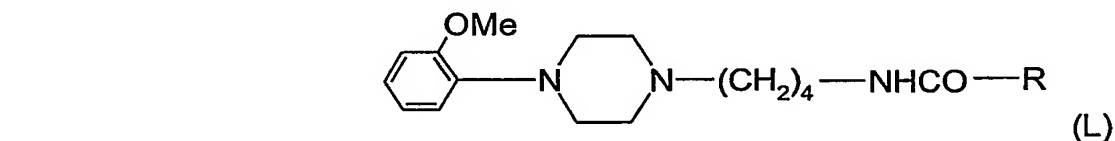
and NPY Y5 receptor inhibition related disorders such as memory disorders, epilepsy, dyslipidemia and depression. US Patent no. 6,048,900, published after the priority date of the present invention discloses the same information.

- 5 Journal Of Medicinal Chemistry, Vol. 31, 1968-1971, 1988 discloses certain aryl piperazines compounds, which fall outside the present invention, as 5HT-1a Serotonin Ligands as potential CNS agents. Specifically disclosed are compounds of formula (K)



where Ar=Ph and R = Ph, Ar= 2-OMePh and R =Ph and Ar=2-pyrimidyl and R=Ph.

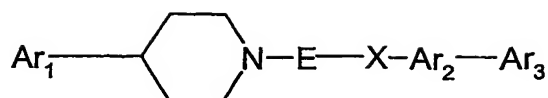
- 15 Journal Of Medicinal Chemistry, Vol. 34, 2633-2638, 1991 discloses aryl piperazines having reduced $\alpha 1$ adrenergic affinity. Specifically disclosed is the compound (L)



where R is 4-(BnO)-phenyl, which falls outside the scope of the present invention.

25 The present invention provides aryl piperidine derivatives which are particularly useful in treating cardiovascular disorders associated with elevated levels of circulating LDL-cholesterol.

Thus, the present invention provides, as a first aspect, a compound of formula (I)



(I)

wherein

Ar_1 represents

- (i) phenyl, naphthyl, or phenyl fused by a C_{3-8} cycloalkyl, or
- (ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that at least one ring is aromatic,

where Ar_1 bears at least one group independently represented by R^1 and 0-3 groups independently represented by R^3 ;

R^1 is $\text{O}(\text{CH}_2)_n\text{OR}^2$;

R^2 is H or $(\text{CH}_2)_m\text{CH}_3$;

n is 1-4;

m is 0-4;

R^3 is selected from halogen, $-\text{O}-(\text{C}_{0-4} \text{ alkylene})-\text{R}^4$ or $-(\text{C}_{0-4} \text{ alkylene})-\text{R}^4$, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms ;

R^4 represents

- (i) hydrogen, C_{1-4} perfluoroalkyl, C_{1-4} perfluoroalkoxy,
- (ii) phenyl, phenyl fused by a C_{3-8} cycloalkyl, naphthyl or a 5- or 6-membered heteroaromatic group, optionally substituted by one or two groups

- independently selected from halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino and di-C₁₋₄ alkylamino,
- (iii) C₃₋₈cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7 ring atoms, wherein said radical contains a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein said radical may be independently saturated, partially unsaturated, or aromatic, and where the C₃₋₈cycloalkyl or a monocyclic heterocyclyl may bear one or two groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino and di-C₁₋₄ alkylamino, or
- (iv) amino, C₁₋₄ alkylamino or di-C₁₋₄alkylamino;

Ar₂ represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, where each group is optionally substituted by one or two groups independently selected from the group consisting of: C₁₋₄ alkyl, halogen, hydroxy, C₁₋₄ alkoxy, C₁₋₆ acyl, C₁₋₆ acyloxy, amino, C₁₋₄ alkylamino and di-C₁₋₄ alkylamino groups;

Ar₃ represents

- (i) phenyl, naphthyl, or phenyl fused by a C₃₋₈cycloalkyl,
- (ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

where Ar₃ is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkenyloxy, C₁₋₄ perfluoroalkoxy, C₁₋₄ acylamino or an electron withdrawing group selected from the list consisting of: nitrile, nitro, C₁₋₄, C₁₋₄ perfluoroalkyl, C₁₋₄ acyl, C₁₋₄ alkoxycarbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl; di-C₁₋₄ alkylaminocarbonyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylaminosulfonyl and di-C₁₋₄ alkylaminosulfonyl, C₁₋₄ alkylsulfonyl and C₁₋₄alkylsulfoxy;

E represents -C₁₋₆ alkylene-;

X represents -CON(H or C₁₋₄alkyl)- or -N(H or C₁₋₄alkyl)CO-;

5 or a physiologically acceptable prodrug, salt or solvate thereof.

As used herein the term "physiologically acceptable" means a compound which is suitable for pharmaceutical use.

10 Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable inorganic acids for example, hydrochlorides, hydrobromides or sulphates, or with
pharmaceutically acceptable organic acids for example mesylates, lactates and acetates. More suitably, a physiologically acceptable salt of the compounds of
15 general formula (I) is a mesylate salt.

The solvates may, for example, be hydrates.

In addition, prodrugs are also included within the context of this invention.
20 Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention
25 wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I). Further, in the case of a
30 carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like.

References hereinafter to a compound according to the invention include
35 compounds of formula (I) and their physiologically acceptable prodrugs, salts and solvates.

Referring to the general formula (I), alkyl, alkylene and alkoxy include both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl and ethyl groups, examples of alkylene groups include methylene and ethylene groups, whilst examples of alkoxy groups include methoxy and ethoxy groups.

Referring to the general formula (I), alkenyl includes both straight and branched chain saturated hydrocarbon groups containing one double bond. Examples of alkenyl groups include ethenyl or n-propenyl groups.

Referring to the general formula (I), acyl refers to aliphatic or cyclic hydrocarbons attached to a carbonyl group through which the substituent bonds, such as acetyl.

Referring to the general formula (I), phenyl fused by a C₃₋₈cycloalkyl includes bicyclic rings such as 1,2,3,4-tetrahydronaphthyl, which, for the avoidance of doubt, is linked to the rest of the molecule through the aromatic ring.

Referring to general formula (I), a halogen atom includes fluorine, chlorine, bromine or iodine.

Referring to the general formula (I), C₁₋₃perfluoroalkyl and C₁₋₃perfluoroalkoxy includes compounds which the hydrogens have been partially or fully replaced by fluorines, such as trifluoromethyl and trifluoromethoxy or trifluoroethyl.

Referring to the general formula (I), a 5-6 membered heteroaromatic group includes a single aromatic ring system containing at least one ring heteroatom independently selected from O, N and S. Suitable examples include pyridyl and thiazolyl.

Referring to the general formula (I), a C₃₋₈ cycloalkyl group means any single carbocyclic ring system, wherein said ring is fully or partially saturated. Suitable examples include cyclopropyl and cyclohexyl groups.

Referring to the general formula (I), a 3-7 membered heterocycloalkyl group means any single ring system containing at least one ring heteroatom independently selected from O, N and S, wherein said ring is fully or partially saturated.

5

Preferably, Ar₁ represents phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indole, benzofuran or benzothiophene. More preferably, Ar₁ represents phenyl, 1,2,3,4-tetrahydronaphthyl or indole.

10

Where Ar₁ is 1,2,3,4-tetrahydronaphthyl, the link to the piperidine ring is preferably through the 2- position of the 1,2,3,4-tetrahydronaphthyl moiety and mono-substitution by R¹ is in the corresponding 1- position.

15

Where Ar₁ is indole, the link to the piperidine ring is preferably through the 3- position of the indole moiety and mono-substitution by R¹ is in the corresponding 1- position.

20

Where Ar₁ is naphthyl, the link to the piperidine ring is preferably through the 1- or 2- position of the naphthyl moiety and mono-substitution by R¹ is in either the corresponding 2- or 1- positions respectively.

R¹ is preferably O(CH₂)₂OCH₂CH₃ or O(CH₂)₂OH.

25

E is preferably an n-butylene group.

X is preferably a -N(H or C₁₋₄ alkyl)CO- group, more preferably an -N(H)CO- group.

30

Preferably, Ar₂ represents phenyl or a 5-6-membered heteroaromatic group. More preferably Ar₂ represents phenyl, thiazolyl or oxadiazole.

35

Ar₃ is preferably a phenyl or pyridyl group, suitably 2-pyridyl. Ar₃ is preferably substituted by halogen, e.g. chloro or C₁₋₄perfluoroalkyl, e.g. trifluoromethyl, nitrile, C₁₋₄acyl, e.g. acetyl, or C₁₋₄alkylsulfonyl, e.g. methylsulfonyl.

When Ar₃ is phenyl, para- substitution is preferred.

Particularly preferred compounds of the invention include those in which each variable in Formula (I) is selected from the preferred groups for each variable.

5 Even more preferable compounds of the invention include those where each variable in Formula (I) is selected from the more preferred or most preferred groups for each variable.

10 The compounds of the invention are inducers of LDL-r expression and are thus of use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

15 The ability of the compounds of the invention to induce LDL-r expression by human hepatocytes in vitro is determined using a human hepatocarcinoma cell line, Hep G2, as a model system. A reporter gene assay using the LDL-r promoter in front of the reporter gene Luciferase is used as a primary screen.

20 The in vivo profile of the compounds is evaluated by oral administration of the compounds of the invention to fat-fed hamsters. Measurements of VLDL/LDL cholesterol and triglycerides upon treatment allow the activity to be determined.

25 The compounds of the invention are potent and specific inducers of LDL-r expression, which furthermore exhibit good oral bioavailability and duration of action.

Compounds of the invention are of use in the treatment of diseases in which lipid imbalance is important, e.g. atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), coronary heart diseases and obesity.

30 Compounds of the invention are also useful in lowering serum lipid levels, cholesterol and/or triglycerides, and are of use in the treatment of hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia.

The invention therefore provides a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof for use in therapy, in particular in human medicine.

5 There is also provided as a further aspect of the invention the use of a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

10 In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol, comprising administration of an effective amount of a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof.

15 It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

20 Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in
25 medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

30 Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, transdermal, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

35 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with

pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica);
5 disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such
10 liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-
15 p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled
20 release of the active compound.

For buccal administration the composition may take the form of tablets or
lozenges formulated in conventional manner.

For transdermal administration the compounds according to the invention may
25 be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending, and/or colouring agents.

The compounds of the invention may be formulated for parenteral administration
30 by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory
35 agents such as suspending, stabilising and/or dispersing agents. Alternatively,

the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

5 The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

10 Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more
15 dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

20 The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

25 The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

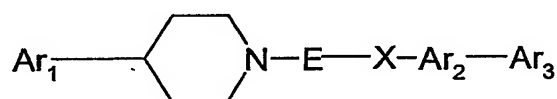
30 For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compositions may contain from 0.1% upwards, e.g. 0.1 - 99% of the active material, depending on the method of administration. A proposed dose of the compounds of the invention is 0.25mg/kg to about 125mg/kg bodyweight per day e.g. 20mg/kg to 100mg/kg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

- 5 The compounds of formula (I) may, if desired, be administered with one or more therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the compounds of formula (I) may be administered in combination with an HMG CoA reductase inhibitor, an agent for inhibition of bile acid transport or fibrates.
- 10
- 15

A compound of formula (I), or a physiologically acceptable prodrug, salt, solvate or derivative thereof, may be prepared by the general methods outlined hereafter. In the following description, the groups Ar_1 , Ar_2 , Ar_3 , R^1 , R^2 , R^3 , R^4 , E and X are as previously defined for compounds of formula (I), unless specified otherwise.

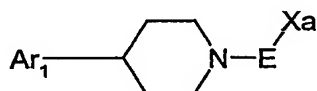
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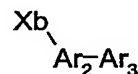
(I)

According to a first general process (A), a compound of formula (I) may be prepared by reaction of a compound of formula (II) with a compound of formula (III)

25



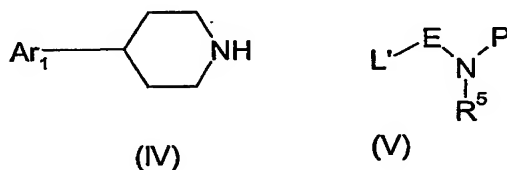
(II)



(III)

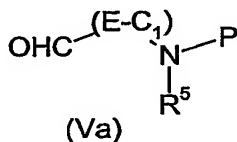
where Xa and Xb are suitable reactants to form a group X. For example, where X is N(H or C₁₋₄ alkyl)CO, Xa is NH₂ or NH(C₁₋₄ alkyl) and Xb is COL where L is OH or a suitable leaving group, such as halide. Such a reaction may be effected under standard amide bond-forming conditions, including those described herein.

A compound of formula (II) where Xa is NH₂ or NH(C₁₋₄ alkyl), may be prepared by reaction of a compound of formula (IV) with a compound of formula (V)



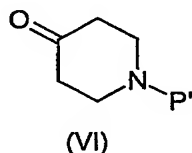
where R⁵ represents H or C₁₋₄alkyl, L' is a suitable leaving group, such as halide, and P is any suitable N-protecting group, under standard alkylation conditions, including those described herein, followed by removal of the protecting group under standard conditions.

A compound of formula (II) where Xa is NH₂ or NH(C₁₋₄ alkyl), may further be prepared by reaction of a compound of formula (IV) with a compound of formula (Va)



where R⁵ represents H or C₁₋₄alkyl, where E-C₁ ('E minus C₁') means that the chain length of group E is one carbon less than that in the resulting compound (II), and P is any suitable N-protecting group, under standard reductive amination conditions, including those described herein, followed by removal of the protecting group under standard conditions.

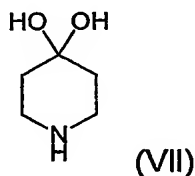
A compound of formula (IV) may be prepared by reaction of a compound $\text{Ar}_1\text{-sal}$, where sal represents the lithium or magnesium ion of Ar_1 , with a compound of formula (VI)



where P' represents a suitable N-protecting group, such as acetyl, benzyl or benzyl-4-oxo-1 carboxylate, followed by the steps of dehydration, reduction of the resulting double bond, and finally, removal of the protecting group P' using standard conditions. Such chemistry has been described, for example, in European Patent Application no. 0630887.

Alternatively, a compound of formula (IV) where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy, may be prepared by reaction of a compound of formula $\text{Ar}_1\text{-Act}$, with a compound of formula (VI) under suitable reaction conditions such as e.g. trifluoroborane or acetic acid and aqueous hydrochloric acid, to form a tetrahydropyridyl ring, followed by reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group, P' under standard conditions.

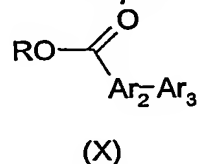
Alternatively, a compound of formula (IV) where where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy, may be prepared by reaction of a compound of formula $\text{Ar}_1\text{-Act}$, with a compound of formula (VII)



under suitable reaction conditions such as e.g. acetic acid and aqueous hydrochloric acid to form a tetrahydropyridyl ring, followed by suitable N-

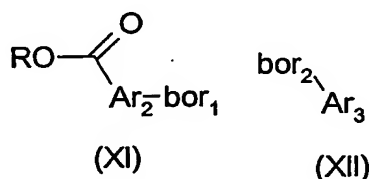
protection, then reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group.

- 5 A compound of formula (III) may be prepared by standard methods including, where Xb is CO₂H, deprotection of a compound of formula (X)



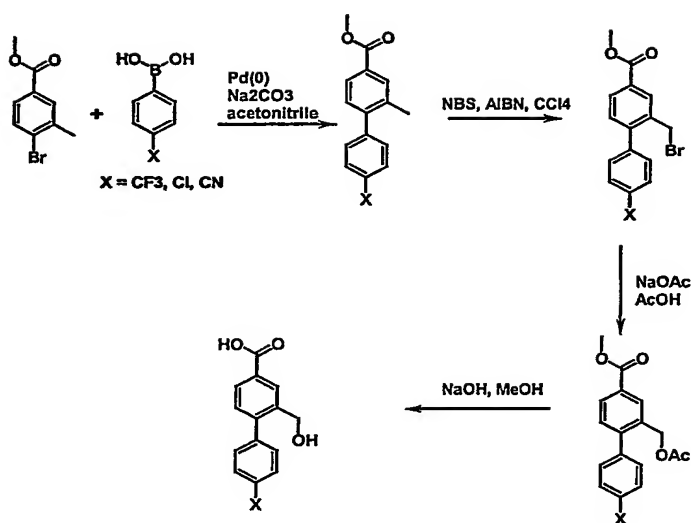
where R is a suitable carboxylic acid protecting group, such as methyl and ethyl.

- 10 A compound of formula (X) where R is H or a suitable protecting group, may be prepared by reaction of a compound of formula (XI), with a compound of formula (XII)

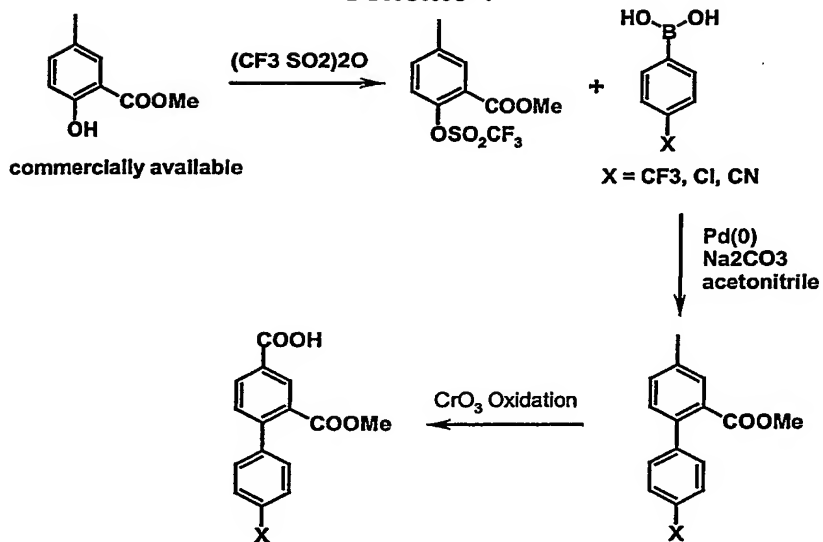


- 15 where bor₁ represents a boronic acid group or a halide, e.g. bromide or iodide, and bor₂ represents a suitable boronic acid group or a halide, e.g. bromide or iodide for coupling, under conditions suitable for boronic acid coupling, e.g. using palladium (0) and sodium carbonate.

- 20 Schemes 1 and 2 below illustrate examples of the preparation of compounds of formula (X) wherein Ar₂ is phenyl.



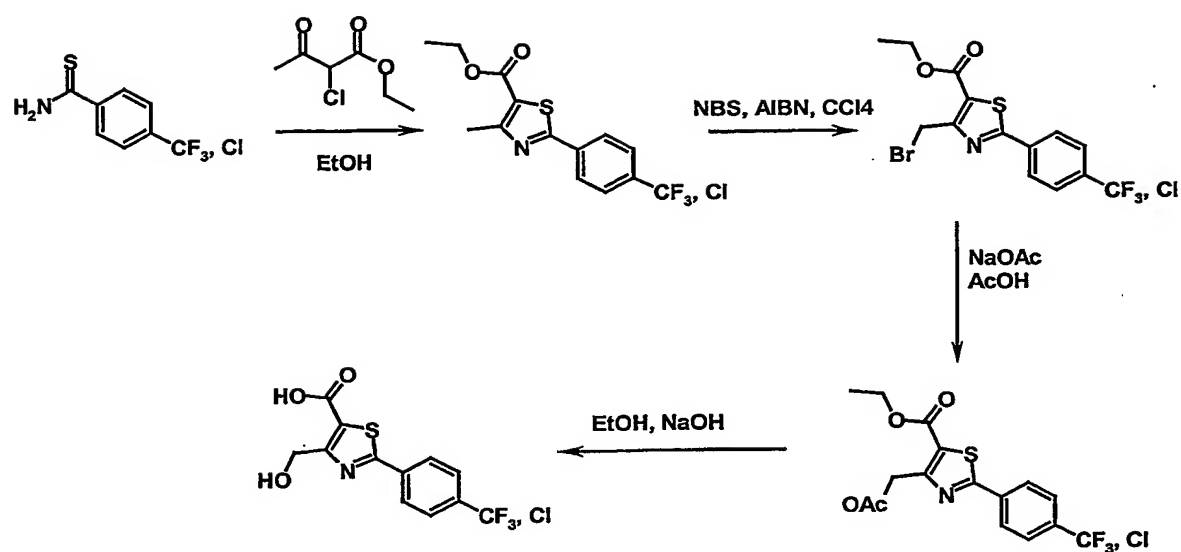
Scheme 1



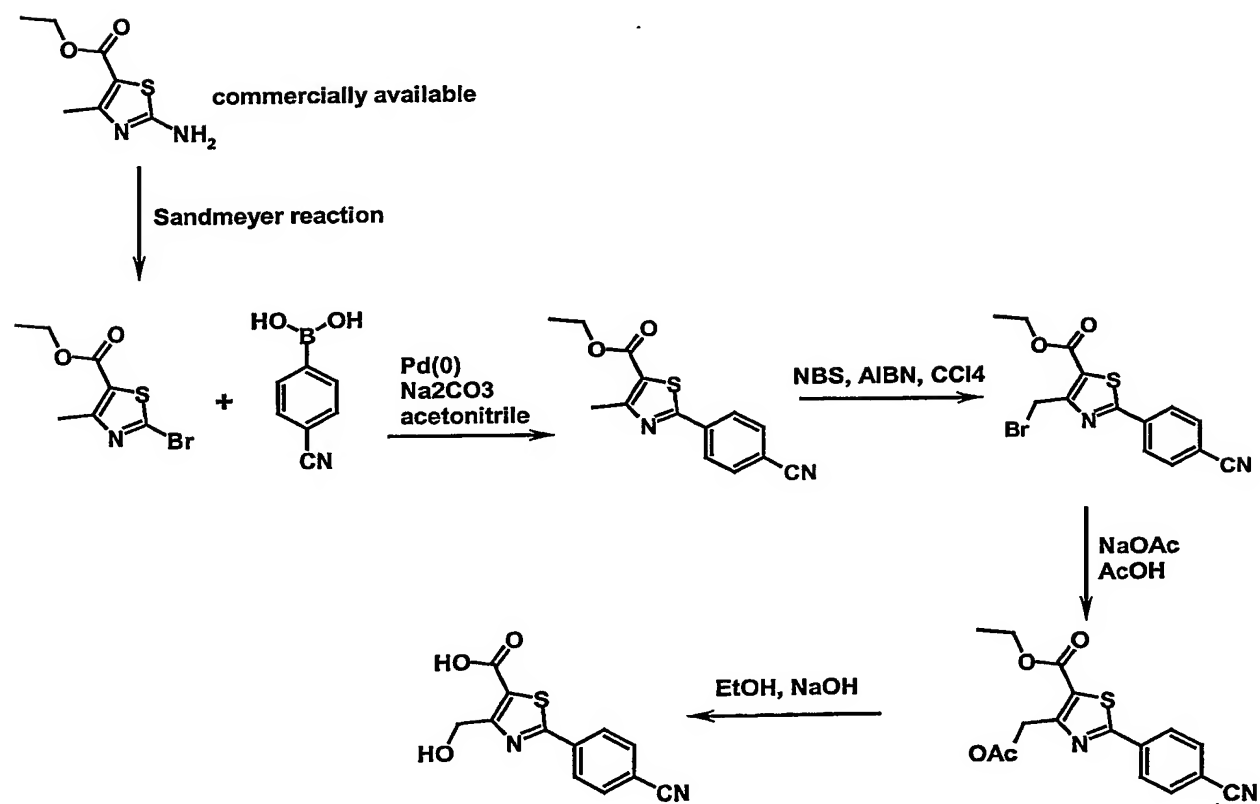
Scheme 2

- 5 Schemes 3 and 4 show examples of the preparation of compounds of formula (X) when Ar₂ is a 5-6-membered heteroacromatic group.

21



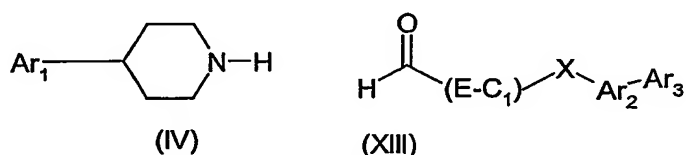
Scheme 3



Scheme 4

It will be apparent to a person skilled in the art that further compounds of formula (X) may be synthesised in an analagous fashion to that illustrated in Schemes 1-4.

- 5 According to a second general process (B), a compound of formula (I) may be prepared by reaction of a compound of formula (IV) with a compound of formula (XIII)

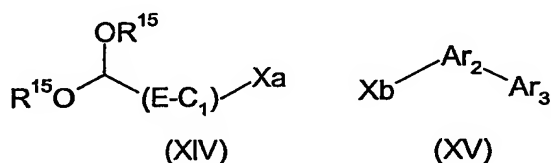


10

where E-C₁ ('E minus C₁') means that the chain length of group E is one carbon less than that in the resulting compound (I), under standard reductive amination conditions, e.g. sodium triacetoxyborohydride and acetic acid in a suitable solvent, such as dichloromethane.

15

A compound of formula (XIII) may be prepared by reaction of a compound of formula (XIV) with a compound of formula (XV)



20

where R¹⁵ is a suitable alkyl protecting group for oxygen, such as methyl, and Xa and Xb are suitable reactants to form a group X, as defined hereinbefore, followed by removal of the protecting group, under acidic conditions.

25

According to a third general process (C), a compound of formula (I) may be prepared by reaction of a different compound of formula (I), by well known methods. For example a compound of formula (I) where Ar₁ is substituted by C₁₋₄ alkoxy may be prepared from the corresponding compound of formula (I) where the substituent is hydroxy by standard O-alkylation methods.

30

Compounds of formula (V), (VI), (VII), (VIII), (IX), (XI), (XIV) and (XV), are known or may be prepared by standard methods, e.g. as substantially described herein.

5 The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed. J. F. W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene and P M G Wuts (John Wiley and Sons 1991).

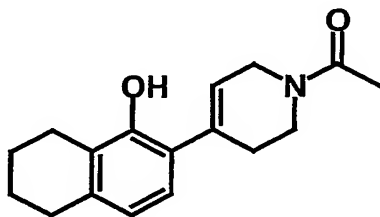
10 Conventional amino protecting groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl.

Conventional carboxylic acid protecting groups include methyl and ethyl groups.

15 The invention is further described with reference to the following non-limiting examples.

20 Abbreviations :

Pd(PPh₃)₄- Tetrakis-(triphenylphosphine)-palladium(0), THF- Tetrahydrofuran, BF₃-Et₂O- Boron trifluoride diethyl etherate, DCM- Dichloromethane, TEA- triethylamine, CH₃CN- Acetonitrile, EtOH- Ethanol, EtOAc- Ethyl acetate, iPr₂O- Di-isopropyl ether, iPrOH- Isopropanol, Pd/C- Palladium on carbon, Et₂O- diethyl ether, Chex- cyclohexane, MeOH- Methanol, DMF- Dimethyl formamide, EDCl- 1-(3-dimethylaminopropyl)-, ethylcarbodiimide hydrochloride, HOBt- 1-Hydroxybenzotriazole, rt- Room temperature, AcOH- Acetic acid, NaOH- Sodium hydroxide, KOH- potassium hydroxide, HCl- Hydrochloric acid, AcOH- Acetic acid, NaH- Sodium hydride, Na₂SO₄- Sodium sulfate, CCl₄- Carbon tetrachloride, AIBN- 2,2'-Azobis(2-methylpropionitrile), K₂CO₃- Potassium carbonate, Na₂CO₃- Sodium carbonate, NaCl- Sodium chloride, TMAD- N,N,N',N'-tetramethylazodicarboxamide, POCl₃- Phosphorus oxychloride, DME-Dimethyl ether, Cs₂CO₃- Cesium carbonate, CrO₃- Chromium(VI) oxide, BBr₃- Boron tribromide.

Intermediate 1**1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone**

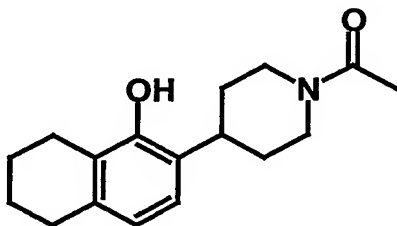
5

To a solution of 5,6,7,8-tetrahydro-naphthalen-1-ol (20.0 g, 0.135 mol) and 1-acetyl-4-piperidone (22.84 g, 1.2 eq.) in THF (400 mL), was added dropwise $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (68 mL, 4.0 eq). The mixture was stirred at 100°C for 2 hours, and 14 hours at room temperature. The mixture was treated with a 1N HCl solution (400 mL). The resulting solution was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give an oil which was recrystallized in acetonitrile to give the title compound (24.2 g, 89 mmol) as a white crystals in a 66% yield.

10

GC/MS: M^+ $\text{C}_{17}\text{H}_{20}\text{NO}_2$ 271

15

Intermediate 2**1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-ethanone**

20

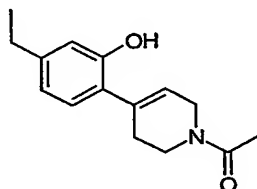
To a solution of intermediate 1 (9.4 g, 34.7 mmol) in EtOH (300 mL) was added Pd/C, 10% (0.9 g) and the reaction was stirred under an atmospheric pressure of hydrogen at 25°C for 24 hours. The mixture was filtered through a bed of celite. The filtrate was evaporated under reduced pressure to give the title compound (9.6 g, 35 mmol) as a white foam.

25

GC/MS: M^+ $C_{17}H_{22}NO_2$ 273

Intermediate 3

5 **1-[4-(4-Ethyl-2-hydroxy-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone**

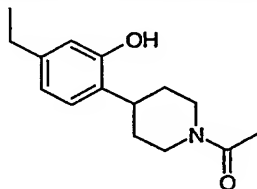


10 The same method was employed as in the preparation of intermediate 1 but starting from 3-ethyl-phenol gave the title compound as a pink solid in a quantitative yield.

GC/MS: M^+ $C_{15}H_{19}NO_2$ 245

Intermediate 4

15 **1-[4-(4-Ethyl-2-hydroxy-phenyl)-piperidin-1-yl]-ethanone**

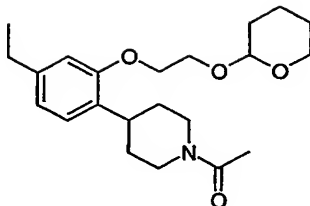


20 The same method was employed as in the preparation of intermediate 2 but starting from intermediate 3 gave the title compound as a solid in a 89% yield.

GC/MS: M^+ $C_{15}H_{21}NO_2$ 247

Intermediate 5

25 **1-(4-{4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-ethanone**

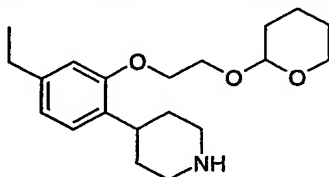


To a solution of intermediate 4 (5 g, 20 mmol) in acetone (200 mL) was added K_2CO_3 (5.52 g, 2 eq.) and the 2-(2-bromo-ethoxy)-tetrahydro-pyran (4.58 mL, 1.5 eq.). The mixture was stirred to reflux for 48 hours and the solvent evaporated. The residue was diluted in DCM and washed with water. The organic layer was dried over Na_2SO_4 and filtered to give the title compound (11.0 g, 27 mmol) as yellow oil in a quantitative yield after chromatography using DCM/MeOH (98/02) as eluent.

GC/MS: M^+ $C_{22}H_{33}NO_4$ 290 (M-Tetrahydropyran)

Intermediate 6

4-{4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidine

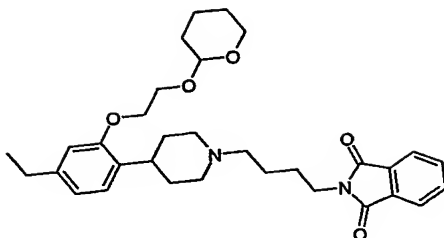


To a solution of intermediate 5 (1.0 eq) in EtOH was added a NaOH/ H_2O (1/1) solution and the mixture was stirred to reflux for 24 hours. The solvent was evaporated, water added and the residue extracted with DCM. The organic layer was dried over Na_2SO_4 and the solvent evaporated to give the title compound as brown oil in a 73.4%.

GC/MS: M^+ $C_{20}H_{31}NO_3$ 333

Intermediate 7

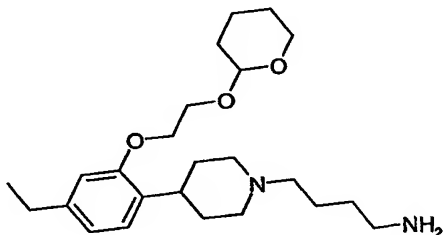
2-[4-(4-{4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-butyl]-isoindole-1,3-dione



To a solution of intermediate 6 (1.0 eq) in acetone was added K_2CO_3 (2.0 eq.) and 4-bromobutyl-phthalimide (1.0 eq.). The mixture was stirred to reflux for 6 hours and filtered. The filtrate was evaporated and the residue was purified by
5 flash chromatography using DCM/MeOH (95/05) as eluent to give the title compound as a brown oil in a quantitative yield.

1H NMR ($CDCl_3$, 300 MHz) δ 7.8 (m, 2H), 7.6 (m, 2H), 7 (d, 1H), 6.6 (d, 1H), 6.5 (s, 1H), 5.2 (s, 2H), 4.8 (m, 1H), 4.1-1.1 (m, 32H)

10 **Intermediate 8**
4-(4-(4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl)-piperidin-1-yl)-butylamine



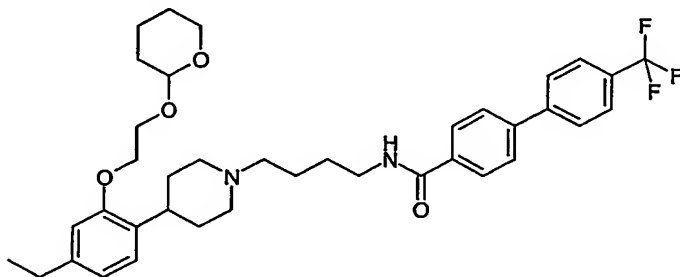
A solution of intermediate 7 (1.0 eq) in MeOH was treated with hydrazine monohydrate (2.0 eq.). The resulting mixture was stirred to reflux for 16 hours.
15 After cooling to rt, and evaporation under reduced pressure the residue was taken up in water and a 1N HCl solution was added until pH=4. Filtration gave yellow solution that was treated with a concentrated NaOH solution. Extraction with DCM, drying over Na_2SO_4 and filtration gave the title compound as a brown
20 oil in a 78% yield.

1H NMR ($CDCl_3$, 300 MHz) δ 7.1 (d, 1H), 6.7 (d, 1H), 6.6 (s, 1H), 5.2 (s, 2H), 4.8 (m, 1H), 4.1-1.1 (m, 34H)

Intermediate 9

4'-Trifluoromethyl-biphenyl-4-carboxylic acid [4-(4-{4-ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-butyl]-amide

5



10

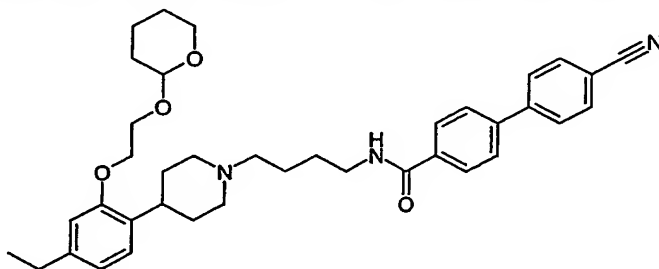
A solution of intermediate 8 (1.0eq) in DMF was treated with 4'-trifluoromethyl-biphenyl-4-carboxylic acid (1.0 eq.), EDCI (1.5 eq.), HOBT (1.5 eq.) and TEA (1.5 eq.). The resulting mixture was stirred for 24 hours at rt, and the solvent evaporated. The residue was diluted with DCM and washed with water and with a 1N NaOH solution. The organic layer was dried over Na₂SO₄ and evaporated off. After purification by flash chromatography using DCM/MeOH (95/5) as eluent, the title compound was obtained as white crystals in a 27% yield.

LC/MS: M+H C₃₈H₄₈F₃N₂O₄ 653

15

Intermediate 10

4'-Cyano-biphenyl-4-carboxylic acid [4-(4-{4-ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-butyl]-amide



20

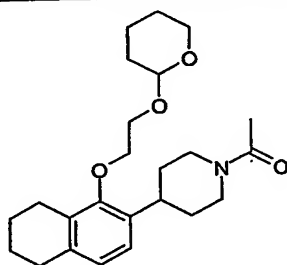
The same method was employed as in the preparation of intermediate 9 but starting from the available 4'-cyano-biphenyl-4-carboxylic acid gave the title compound as a yellow oil in a 20% yield.

LC/MS: M+H $C_{38}H_{48}N_3O_4$ 610

5

Intermediate 11

1-(4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-ethanone



10

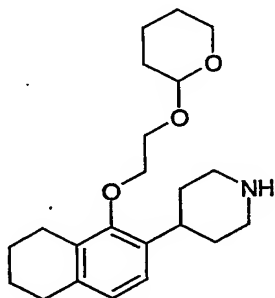
The same method was employed as in the preparation of intermediate 5 but starting from intermediate 2 gave the title compound as a yellow oil in a 95% yield.

LC/MS: M+H $C_{24}H_{36}NO_4$ 402

15

Intermediate 12

4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidine



The same method was employed as in the preparation of intermediate 6 but starting from intermediate 11 gave the title compound as yellow oil in a quantitative yield.

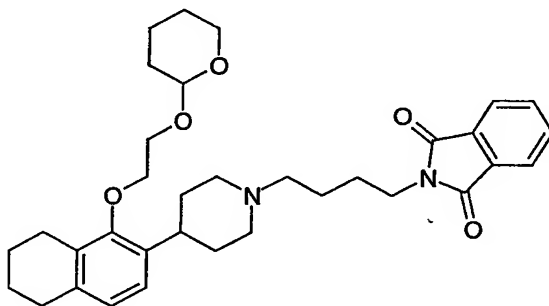
LC/MS: M+H C₂₂H₃₄NO₃ 360

5

Intermediate 13

2-[4-(4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butyl]-isoindole-1,3-dione

10



The same method was employed as in the preparation of intermediate 7 but starting from intermediate 12 gave the title compound as a yellow oil in a 93% yield.

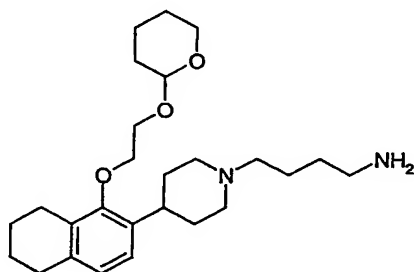
15

LC/MS: M+H C₃₄H₄₅N₂O₅ 561

Intermediate 14

4-(4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butylamine

20

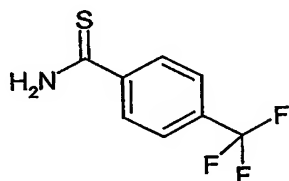


The same method was employed as in the preparation of intermediate 8 but starting from intermediate 13 gave the title compound as a yellow oil (contained 30% of formed pyridazine dione).

5 LC/MS: M+H C₂₆H₄₃N₂O₃ 431

Intermediate 15

4-Trifluoromethyl-thiobenzamide

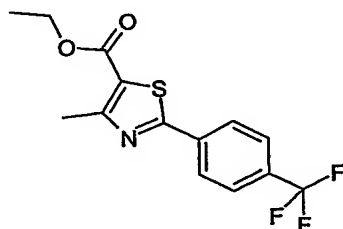


A solution of α,α,α -trifluoro-p-tolunitrile (603.5 g, 3.53 mol) in dry DMF (2 L) under N₂ was heated at 70°C and the thioacetamide (505 g, 1.9 eq.) was added. The reaction mixture was treated with HCl gas for 15 minutes and stirred at 95°C for 6 hours. This treatment was repeated 3 times and the mixture stirred at rt for 24 hours. After cooling at 0°C, water was added and the residue extracted with diethyl ether (4 L). The organic layer was washed with water (3 L), dried over Na₂SO₄ and the solvent evaporated. The brownish powder was washed with pentane (3 L) to give the title compound (530.3g, 2.59 mol) as a brown solid in a 73% yield.

20 GC/MS: M⁺ C₈H₆F₃NS 205

Intermediate 16

4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester

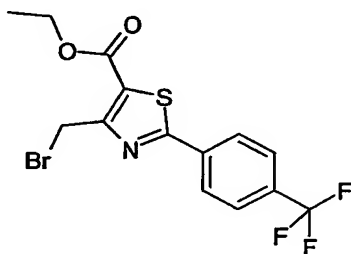


To a solution of intermediate 15 (530.3 g, 2.59 mol) in EtOH (2.6 L) was added 2-chloro-3-oxo-butyric acid ethyl ester (465 mL, 1.3 eq.). The mixture was stirred at rt for 7 hours and at 70°C for 14 hours. After cooling at 0°C, the precipitate was filtered off and washed with cold EtOH (500 mL) to give the title compound (573.0 g, 1.89 mol) as a beige powder in a 73% yield.

¹H NMR (CDCl₃, 300 MHz) δ 7.9 (d, 2H), 7.6 (d, 2H), 4.3 (q, 2H), 2.65 (s, 3H), 1.25 (t, 3H).

Intermediate 17

4-Bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester

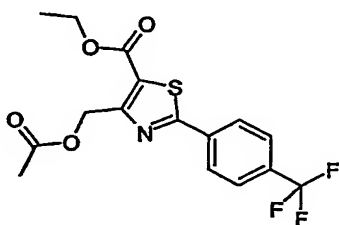


To a solution of intermediate 16 (15.75 g, 50.0 mmol) in CCl₄ was added slowly N-bromosuccinimide (8.9 g, 1.1 eq.) and AIBN (1 g, 10%mol). The mixture was stirred at 80°C for 3 hours, filtered off and the filtrate evaporated. After purification by flash chromatography, using DCM/Cyclohexane (60/40) as eluent, the title compound (4.9 g, 12.5 mmol) was obtained as white solid in a 25% yield.

¹H NMR (CDCl₃, 300 MHz) δ 8.2 (d, 2H), 7.8 (d, 2H), 5.1 (s, 2H), 4.5 (q, 2H), 1.3 (t, 3H)

Intermediate 18

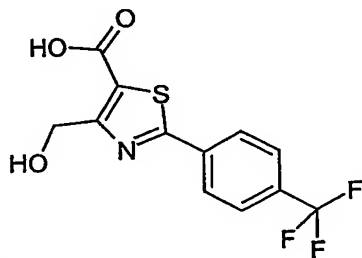
4-Acetoxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester



To a solution of intermediate 17 (4.9 g, 12.5 mmol) in AcOH (15 mL) was added sodium acetate (2.0 g, 2eq.). The mixture was stirred to reflux for 14 hours, and after cooling at rt, the mixture was diluted with water (150 mL) and extracted with diethyl ether (250 mL). The organic layer was washed with a 1 N NaOH solution, dried over Na₂SO₄ and the solvent evaporated. The title compound (3.24 g, 8.7 mmol) was obtained as white crystals in a 72% yield.
MP: 82°C

Intermediate 19

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid

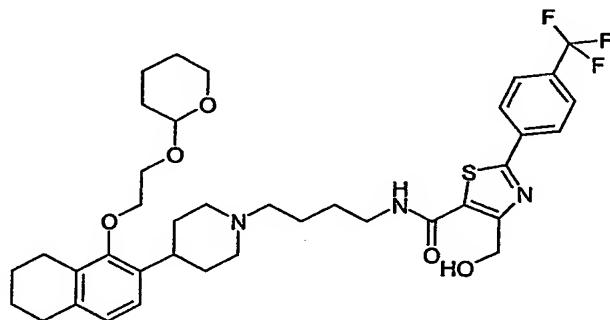


To a solution of intermediate 18 (3.24 g, 8.7 mmol) in EtOH/H₂O (40 mL/20mL) was added the NaOH (1.4 g, 4 eq.) and the mixture was stirred to reflux for 2 hours. After partial evaporation, water (100 mL) was added and treated with a concentrated HCl solution to obtain pH = 1. The precipitate was filtered off, washed with water and dried to give the title compound (2.38 g, 7.8 mmol) as white solid in a 90% yield.
MP: 250-252 °C

Intermediate 20

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid [4-(4-{1-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butyl]-amide

5



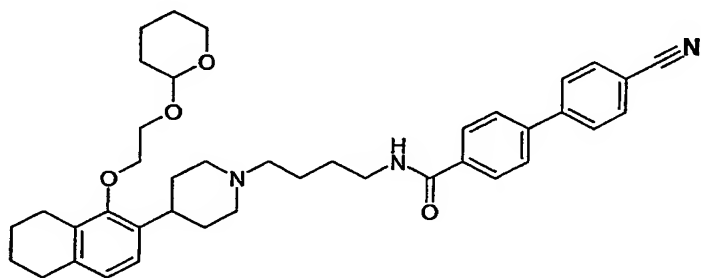
The same method was employed as in the preparation of the intermediate 9 but starting from intermediate 14 and intermediate 19 gave the title compound as a beige powder in a 28% yield.

MP: 146-148°C

10

Intermediate 21

4'-Cyano-biphenyl-4-carboxylic acid [4-(4-{1-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butyl]-amide

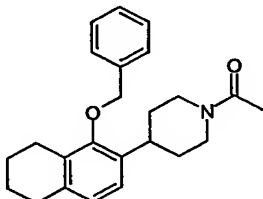


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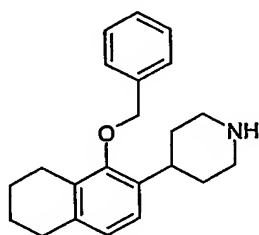
The same method was employed as in the preparation of intermediate 9 but starting from intermediate 14 and 4'-cyano-biphenyl-4-carboxylic acid gave the title compound as white oil in a 62% yield.

LC/MS: M+H C₄₀H₄₉N₃O₄ 636

20

Intermediate 22**1-[4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-ethanone**

- 5 A solution of intermediate 2 (11 g, 40 mmol), K_2CO_3 (19.0 g, 1.5 eq.) in methyl ethyl ketone (150 mL) was stirred at 80°C for 10 minutes. Benzyl bromide (7.7 g, 1.1 eq.) was added and the mixture was stirred to reflux for 2.5 hours. After filtration, the filtrate was evaporated and the residue washed with water, extracted with ether and evaporated off. The solid was washed with iPr_2O to
- 10 give the title compound (9.5 g, 26.2 mmol) as beige crystals in a 66% yield. MP: 108-110 °C

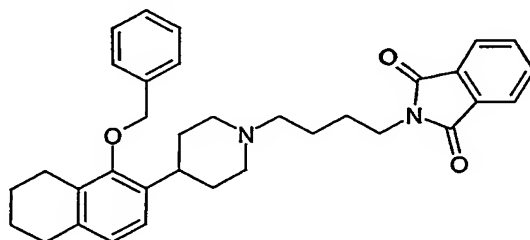
Intermediate 23**4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidine**

The same method was employed as in the preparation of intermediate 6 but starting from intermediate 22 gave the title compound as oil in a 98% yield directly used in the next step without purification.

20 LC/MS: M+H $C_{22}H_{28}NO$ 322

Intermediate 24

2-[4-[4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl]-isoindole-1,3-dione



5

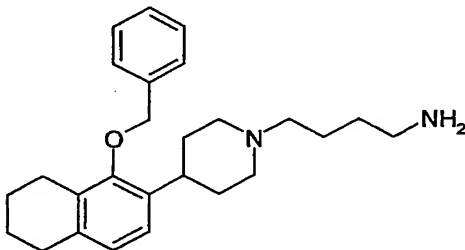
The same method was employed as in the preparation of intermediate 7 but starting from intermediate 23 gave the title compound as an oil in a quantitative yield directly used in the next step without purification.

10 LC/MS: M+H C₃₄H₃₉N₂O₃ 523

Intermediate 25

4-[4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butylamine

15



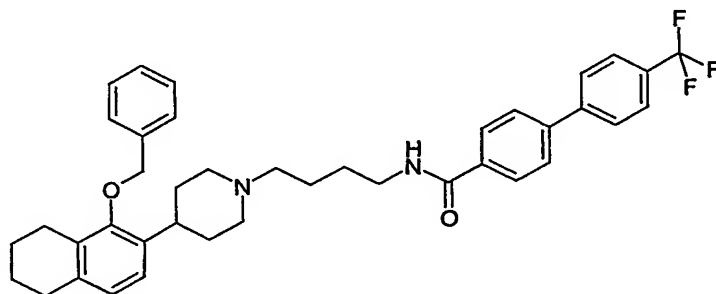
20 The same method was employed as in the preparation of intermediate 8 but starting from intermediate 24 gave the title compound as an oil in a 59% yield directly used in the next step without purification.

LC/MS: M+H C₂₆H₃₇N₂O 393

Intermediate 26

4'-Trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1-benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide

5



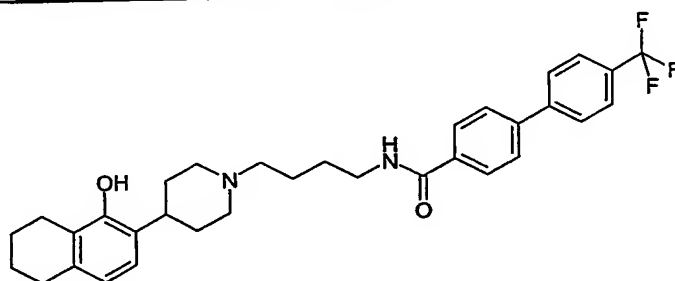
The same method was employed as in the preparation of intermediate 9 but starting from intermediate 25 and 4'-trifluoromethyl-biphenyl-4-carboxylic acid gave the title compound as white crystals in 45% yield after recrystallisation in CH_3CN .
MP: 169-170°C

10

Intermediate 27

4'-Trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1-hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide

15



To a mixture of intermediate 26 (4.0 g, 6.2 mmol) in EtOH (150 mL) was added Pd/C, 10% (0.6 g) and the reaction stirred under an atmospheric pressure of hydrogen at 60°C for 2 hours. The mixture was filtered through a bed of celite.

20

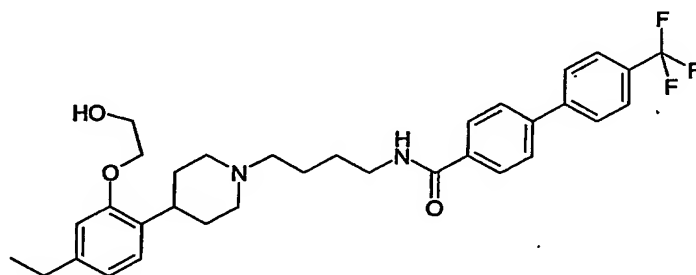
The filtrate was evaporated under reduced pressure to give the title compound (3 g, 5.4 mmol) as a white crystals after crystallisation from EtOH.

MP: 220-222°C

5 EXAMPLES

Example 1 :

4'-Trifluoromethyl-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-butyl)-amide hydrochloride



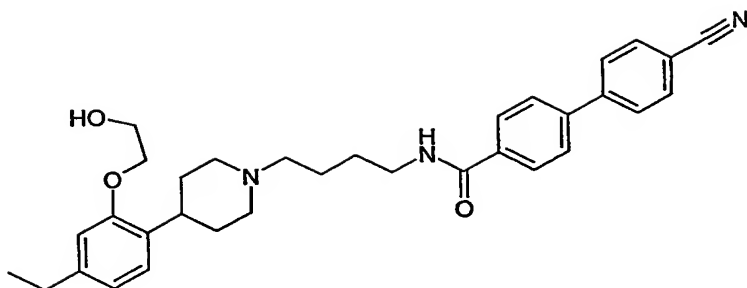
To a solution of intermediate 9 (0.28 g, 0.43 mmol) in MeOH/DCM 50/50 (20 mL) was added a 1N HCl solution (0.9 ml, 2 eq.) and the resulting mixture stirred at rt for 24 hours. The solvent was evaporated off and the residue treated with DCM/*i*Pr₂O to give the title compound (0.080 g, 0.13 mmol) as white crystals in 31% yield.

¹H NMR (CDCl₃, 300 MHz) δ 8.25 (d, 2H), 7.8 (d, 6H), 7.15 (d, 1H), 6.8 (m, 2H), 4.2 (m, 4H), 3.8 (m, 4H), 3.2 (m, 2H), 3-1.8 (m, 15H), 1.3 (t, 3H).

LC/Tof : ES⁺ 569.2946 7.8 ppm

Example 2 :

4'-Cyano-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-butyl)-amide hydrochloride



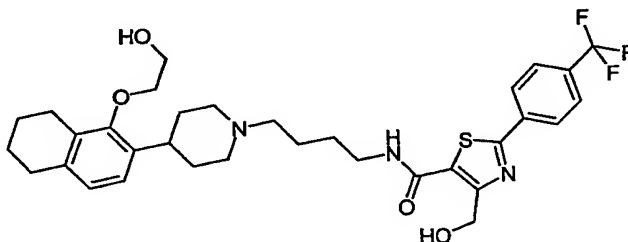
The same method was employed as in the preparation of example 1 but starting from intermediate 10 gave the title compound as white crystals in a 8% yield after recrystallisation in $i\text{Pr}_2\text{O}$.

LC/Tof : ES^+ 526.3093 4.6 ppm

^1H NMR (CDCl_3 , 300 MHz) δ 8.1 (d, 2H), 7.7 (d, 6H), 6.95 (d, 1H), 6.7 (m, 2H), 4.2 (m, 4H), 4.0 (m, 4H), 3.4 (m, 2H), 3.1-1.6 (m, 15H), 1.2 (t, 3H).

Example 3 :

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (4-{4-[1-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide



The same method was employed as in the preparation of example 1 but starting from intermediate 20 gave the title compound as beige crystals in a 39% yield after recrystallisation in CH_3CN .

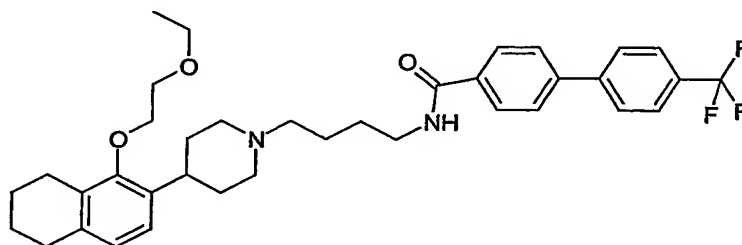
MP: 157-159°C

LC/MS : $\text{M}+\text{H}$ $\text{C}_{33}\text{H}_{41}\text{F}_3\text{N}_3\text{O}_4\text{S}$ 632

Example 4 :

4'-Trifluoromethyl-biphenyl-4-carboxylic acid (4-{4-[1-(2-ethoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide

5

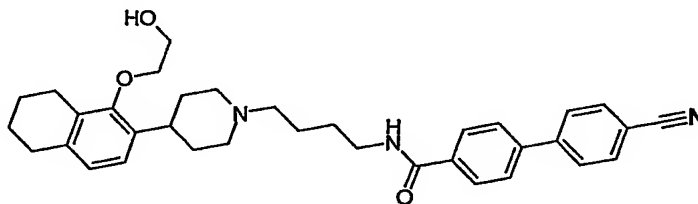


To a solution of TMAD (2.0 eq.) in dry THF under argon was added tributylphosphine (2.2 eq.). The mixture was stirred at rt for 10 minutes. Then intermediate 27 (1.0 eq) and 2-ethoxy-ethanol (1.2 eq.) were added and the mixture was stirred at rt for 48 hours. The water was added and the reaction mixture evaporated off. The residue was taken in water and the precipitate was filtered off. After recrystallisation in CH₃CN, the title compound was obtained as white crystals in a 81% yield.

MP: 190°C

LC/Tof: ES⁺ 623.3485 3.8 ppm**Example 5 :**

4'-Cyano-biphenyl-4-carboxylic acid (4-{4-[1-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide hydrochloride



The same method was employed as in the preparation of example 1 but starting from intermediate 21 gave the title compound as white crystals in a 77% yield after recrystallisation in iPrO₂.

MP: 174°C

LC/tof: ES⁺ 552.3176 9 ppm

Biological Assays

5

In Vitro Assay :

10 HepG₂ cells, stably transfected with a construct comprising the LDL-r promoter and the luciferase reporter gene, were seeded at 50,000 cells/well in 96 well plates. After 1 day, cells were incubated with compounds for 24 hours in RPMI medium containing 2% of lipoprotein-deficient serum. Compounds were tested from 10⁻⁶M to 10⁻⁹M. Cell lysates were prepared and the luciferase activity was measured by the luciferase assay system (Promega). Induction of luciferase activity was calculated taking untreated cells as control and ED₅₀ of each compounds was determined compared to the ED₅₀ of an internal standard.

15

In Vivo Assay :

20 Compounds were prepared for oral administration by milling with 0.5% hydroxypropylmethylcellulose and 5% Tween 80. Hamsters were fed for 2 weeks with a diet containing 0.2% of cholesterol and 10% of coconut oil. Then compounds were administered once a day for 3 days, from 20 to 0.2mg/kg. Plasma lipid levels including total cholesterol, VLDL/LDL cholesterol, VLDL/LDL triglycerides and HDL-cholesterol were determined after ultracentrifugation (density 1.063g/ml to separate VLDL/LDL fraction and HDL fraction) using the Biomerieux enzymatic kit. Reductions in VLDL/LDL cholesterol and TG
25 plasmatic levels were calculated taking solvent treated animals as control and ED₅₀ of each compound was determined.

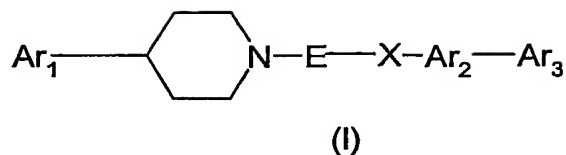
30

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A compound of formula (I)

5



wherein

Ar₁ represents

- 10 (iii) phenyl, naphthyl, or phenyl fused by a C₃₋₈cycloalkyl, or
 (iv) heterocyclyl selected from the group consisting of monocyclic radicals
 and fused polycyclic radicals, wherein said radicals contain a total of from
 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring
 15 heteroatoms independently selected from oxygen, nitrogen and sulfur,
 and wherein individual rings of said radicals may be independently
 saturated, partially unsaturated, or aromatic, provided that at least one
 ring is aromatic,

where Ar₁ bears at least one group independently represented by R¹ and 0-3
 groups independently represented by R³;

20

R¹ is O(CH₂)_nOR²;

R² is H or (CH₂)_mCH₃;

25

n is 1-4;

m is 0-4;

30

R³ is selected from halogen, -O-(C₀₋₄ alkylene)-R⁴ or -(C₀₋₄alkylene)-R⁴, where
 each alkylene group may additionally incorporate an oxygen in the chain, with
 the proviso that there are at least two carbon atoms between any chain
 heteroatoms ;

R⁴ represents

- (v) hydrogen, C₁₋₄ perfluoroalkyl, C₁₋₄perfluoroalkoxy,
(vi) phenyl, phenyl fused by a C₃₋₈cycloalkyl, naphthyl or a 5- or 6-membered
5 heteroaromatic group, optionally substituted by one or two groups
independently selected from halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy,
amino, C₁₋₄ alkylamino and di-C₁₋₄ alkylamino,
(vii) C₃₋₈cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7
10 ring atoms, wherein said radical contains a total of from 1-4 ring
heteroatoms independently selected from oxygen, nitrogen and sulfur,
wherein said radical may be independently saturated, partially
unsaturated, or aromatic, and where the C₃₋₈cycloalkyl or a monocyclic
heterocyclyl may bear one or two groups independently selected from
halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino and di-C₁₋₄
15 alkylamino, or
(viii) amino, C₁₋₄ alkylamino or di-C₁₋₄alkylamino;

Ar₂ represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic
heteroaromatic group, where each group is optionally substituted by one or two
20 groups independently selected from the group consisting of: C₁₋₄ alkyl, halogen,
hydroxy, C₁₋₄ alkoxy, C₁₋₆ acyl, C₁₋₆ acyloxy, amino, C₁₋₄ alkylamino and di-C₁₋₄
alkylamino groups;

Ar₃ represents

- (iii) phenyl, naphthyl, or phenyl fused by a C₃₋₈cycloalkyl,
(iv) heterocyclyl selected from the group consisting of monocyclic radicals
25 and fused polycyclic radicals, wherein said radicals contain a total of from
5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring
heteroatoms independently selected from oxygen, nitrogen and sulfur,
30 and wherein individual rings of said radicals may be independently
saturated, partially unsaturated, or aromatic, providing that at least one
ring is aromatic,

where Ar₃ is optionally substituted by 1-4 groups independently selected from
the group consisting of: hydroxy, alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkenyloxy,
35 C₁₋₄ perfluoroalkoxy, C₁₋₄ acylamino or an electron withdrawing group selected

from the list consisting of: nitrile, nitro, C₁₋₄, C₁₋₄ perfluoroalkyl, C₁₋₄ acyl, C₁₋₄ alkoxy carbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl; di-C₁₋₄ alkylaminocarbonyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylaminosulfonyl and di-C₁₋₄ alkylaminosulfonyl, C₁₋₄ alkylsulfonyl and C₁₋₄alkylsulfoxy;

5

E represents -C₁₋₆ alkylene-;

X represents -CON(H or C₁₋₄alkyl)- or -N(H or C₁₋₄alkyl)CO-;

10

or a physiologically acceptable prodrug, salt or solvate thereof.

2. A compound selected from

15

4'-Trifluoromethyl-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-pentyl)-amide hydrochloride;

4'-Cyano-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-pentyl)-amide hydrochloride;

20

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (4-{4-[3-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide;

4'-Trifluoromethyl-biphenyl-4-carboxylic acid (4-{4-[1-(2-ethoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide;

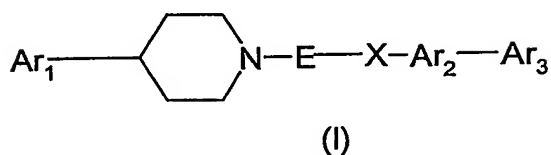
4'-Cyano-biphenyl-4-carboxylic acid (4-{4-[1-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide hydrochloride;

25

or a physiologically acceptable salt, solvate or derivative thereof.

ABSTRACT

5 The invention relates to a compound of formula (I)



wherein

Ar₁ represents

- 10 (v) phenyl, naphthyl, or phenyl fused by a C₃₋₈cycloalkyl, or
 (vi) heterocyclyl selected from the group consisting of monocyclic radicals
 and fused polycyclic radicals, wherein said radicals contain a total of from
 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring
 15 heteroatoms independently selected from oxygen, nitrogen and sulfur,
 and wherein individual rings of said radicals may be independently
 20 saturated, partially unsaturated, or aromatic, provided that at least one
 ring is aromatic,

where Ar₁ bears at least one group independently represented by R¹ and 0-3
 groups independently represented by R³;

20 R¹ is O(CH₂)_nOR²;

R² is H or (CH₂)_mCH₃;

25 n is 1-4;

m is 0-4;

30 R³ is selected from halogen, -O-(C₀₋₄ alkylene)-R⁴ or -(C₀₋₄alkylene)-R⁴, where
 each alkylene group may additionally incorporate an oxygen in the chain, with
 the proviso that there are at least two carbon atoms between any chain
 heteroatoms ;

R⁴ represents

- (ix) hydrogen, C₁₋₄ perfluoroalkyl, C₁₋₄perfluoroalkoxy,
(x) phenyl, phenyl fused by a C₃₋₈cycloalkyl, naphthyl or a 5- or 6-membered
5 heteroaromatic group, optionally substituted by one or two groups
independently selected from halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy,
amino, C₁₋₄ alkylamino and di-C₁₋₄ alkylamino,
(xi) C₃₋₈cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7
10 ring atoms, wherein said radical contains a total of from 1-4 ring
heteroatoms independently selected from oxygen, nitrogen and sulfur,
wherein said radical may be independently saturated, partially
unsaturated, or aromatic, and where the C₃₋₈cycloalkyl or a monocyclic
heterocyclyl may bear one or two groups independently selected from
15 halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, amino, C₁₋₄ alkylamino and di-C₁₋₄
alkylamino, or
(xii) amino, C₁₋₄ alkylamino or di-C₁₋₄alkylamino;

Ar₂ represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic
heteroaromatic group, where each group is optionally substituted by one or two
20 groups independently selected from the group consisting of: C₁₋₄ alkyl, halogen,
hydroxy, C₁₋₄ alkoxy, C₁₋₆ acyl, C₁₋₆ acyloxy, amino, C₁₋₄ alkylamino and di-C₁₋₄
alkylamino groups;

Ar₃ represents

- (v) phenyl, naphthyl, or phenyl fused by a C₃₋₈cycloalkyl,
(vi) heterocyclyl selected from the group consisting of monocyclic radicals
and fused polycyclic radicals, wherein said radicals contain a total of from
5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring
heteroatoms independently selected from oxygen, nitrogen and sulfur,
30 and wherein individual rings of said radicals may be independently
saturated, partially unsaturated, or aromatic, providing that at least one
ring is aromatic,

where Ar₃ is optionally substituted by 1-4 groups independently selected from
the group consisting of: hydroxy, alkyl, C₁₋₄ alkoxy, C₂₋₄ alkenyl, C₂₋₄ alkenyloxy,
35 C₁₋₄ perfluoroalkoxy, C₁₋₄ acylamino or an electron withdrawing group selected

from the list consisting of: nitrile, nitro, C₁₋₄, C₁₋₄ perfluoroalkyl, C₁₋₄ acyl, C₁₋₄ alkoxy carbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl; di-C₁₋₄ alkylaminocarbonyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylaminosulfonyl and di-C₁₋₄ alkylaminosulfonyl, C₁₋₄ alkylsulfonyl and C₁₋₄ alkylsulfoxy;

5

E represents -C₁₋₆ alkylene-;

X represents -CON(H or C₁₋₄alkyl)- or -N(H or C₁₋₄alkyl)CO-;

10

or a physiologically acceptable prodrug, salt or solvate thereof.

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